Conclusions: The prolonged intra-articular inhibition of IL-1 reduced the severity of arthritic changes in both cartilage and joint tissue. However, the inhibition of TNF-α resulted in detrimental bone morphological changes, loss of cartilage, and inflammation of joint tissue. This study shows a novel reduction in post-trauma inflammation and demonstrates utility for an injectable drug depot for clinical intra-articular applications in the treatment of joint trauma.

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IDENTIFICATION OF THE PATIENTS WHO RESPOND SAFELY AND OPTIMALLY TO INTERVENTION WITH BIOLOGICS; LESSON LEARNED FROM RHEUMATOID ARTHRITIS

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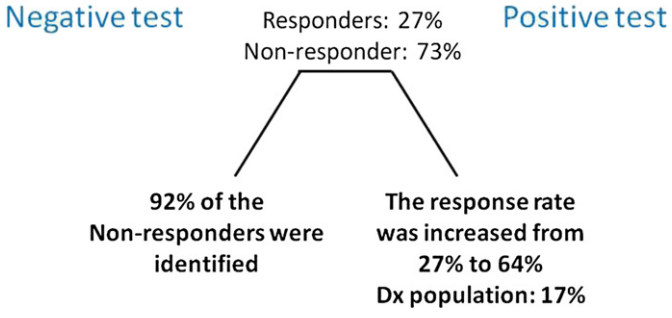
Purpose: Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized debilitating joint destruction, if not treated aggressively in the patient in most need of treatment. Personalized health care is needed and tested in RA, as response rates are low compared to the potential side effects and cost of treatment. Thus lessons on patient segregation can be learned and used in other joint diseases, such as osteoarthritis (OA). We investigated whether tissue-specific, serum-based biomarkers measured at baseline or after 1 dose could identify "super responders" to 4 mg/kg tocilizumab in patients with moderate to severe RA on a methotrexate background enrolled in the LITHE study.
Methods: The LITHE biomarker study (n=740) was a phase III study of 4 and 8mg/kg TCZ in combination with MTX. Patients were separated into ACR50 (week 52) responders and non-responder and serum biomarkers were measured at baseline and week 4. Following tissue-specific biomarkers were measured; C3M (synovial turnover), CRPM (connective tissue inflammation), C2M (cartilage degradation), CTx (bone resorption), osteocalcin (bone formation), CRP (acute phase reactant) and MMP3 (proteolytical activity). ROC was use to find the optimal cut-offs for the biomarkers at baseline and change from baseline to week4. CART analysis was used to segregate patients and 2x2 contingency test was used for identifying response rates.
Results: A simple combination of 4 baseline markers (C1M, C3M, MMP-3 and CRPM) increased the response rates (ACR50 at week 52) from 27 to 54%, while restricting the patient population to 22 %. When including the change from baseline to 4 weeks of cartilage degradation or bone formation, patient benefit was enriched to 64 %, while allowing continued treatment of 17% of patients and referral of 92% of the non-responders earlier to other possible interventions (figure).
Conclusions: By using a combination of simple serological markers, response rates were more than doubled in so-called "IL-6 super responders". This may assist in identification of the patients, in any inflammatory disease, who respond most optimally to given interventions, with fewer AEs, and thus provide a stronger risk/benefit/cost value proposition to patients and payers.



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IDENTIFICATION OF FIBROBLAST GROWTH FACTOR-18 AS A MOLECULE TO PROTECT AND REGENERATE ARTICULAR CARTILAGE

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Purpose: Aiming at the disease-modifying treatment of osteoarthritis (OA), we sought to identify genes that maintain the homeostasis of adult articular cartilage and regenerate its lesions by gene expression profile analyses.
Methods: We initially performed two sets of microarray analyses. First, to identify genes involved in maintenance of articular cartilage, we compared gene expression profiles between adult articular (AA) and adult growth plate (AG) cartilages in 10-week-old rats. Second, to identify genes involved in regeneration of articular cartilage, we compared the profiles between infant superficial (IS) and infant deep (ID) layers of epiphyseal cartilage in 6-day-old rats. For genes which were up-regulated ≥10-fold both in AA than AG and in IS than ID, we performed real-time RT-PCR for the confirmation. In vivo expression of the identified gene was examined by immunohistochemistry of articular and growth plate cartilage of 14-week-old rats. The therapeutic effect was examined in the experimental OA model by surgical induction of instability in the knee joints of adult rats. To learn the underlying mechanism, the protective ability of articular cartilage was assessed by measuring the amount of sulfated glycosaminoglycan (sGAG) released into the medium in the ex vivo culture of bilateral femoral heads of 3-week-old mice. Proliferation and migration were analyzed in the cultures of mouse articular chondrocytes using Cell Counting Kit-8 and Oris Cell Migration assay systems, respectively. Expression levels of catabolism-related factors (Mmp9, Mmp13, Adamts4, Adamts5, Timp1, Timp2, and Timp3) and anabolism-related factors (Col2a1 and aggrecan) in the cultures of mouse femoral heads and mouse articular chondrocytes were analyzed by real-time RT-PCR.
Results: Microarray analyses revealed that 40 and 186 genes had ≥10-fold higher expression ratios of AA/AG and IS/ID, respectively, and 16 genes showed ≥10-fold of both AA/AG and IS/ID ratios. The ratios of the 16 genes were confirmed to be ≥10 fold by real-time RT-PCR analysis. Among them three genes were expressed more strongly in AA than in IS. In these three genes, fibroblast growth factor-18 (Fgf18) was the extracellular and secreted factor of which the AA/AG ratio was the highest in the microarray analysis. Immunohistochemistry showed that Fgf18 was strongly expressed in the articular cartilage chondrocytes of adult rats but was hardly detected in the growth plate cartilage. In the rat surgical OA model, a once-weekly intra-articular injection of recombinant human (rh) FGF18 given 3 weeks post-surgery prevented cartilage degeneration in a dose-dependent manner at 6 and 9 weeks after surgery, with a significant effect at 10 μg/week of rhFGF18. As an underlying mechanism, rhFGF18 suppressed the sGAG release into the culture medium in the ex vivo culture of mouse femoral heads. Furthermore, rhFGF18 accelerated proliferation and migration of cultured mouse articular chondrocytes. Among catabolic and anabolic factors, rhFGF18 decreased Adamts4 and increased Timp1 expressions in the cultures of mouse femoral heads and murine articular chondrocytes, while it decreased Col2a1 and aggrecan expressions in both cultures.
Conclusions: The present gene expression profiling analysis identified Fgf18 as a molecule to protect and regenerate adult articular cartilage, causing prevention of OA development by the intra-articular injection in a rat model. This effect may be mediated by inhibition of cartilage catabolism, and acceleration of proliferation and migration of articular chondrocytes, indicating a possible disease-modifying OA treatment.

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MICRORNAS ARE PROGNOSTIC MARKERS FOR THE CHONDROGENIC POTENTIAL OF MSCS

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Purpose: The capacity of mesenchymal stromal cells (MSCs) to differentiate into chondrocytes as well as to function as trophic mediators restoring joint homeostasis make them a promising cell source for a disease modifying treatment in osteoarthritis. MSCs can be easily harvested from various locations of the body, including amongst others bone marrow, periosteum, synovium, synovial fluid, adipose tissue, buccal fat pad, infrapatellar fat pad and osteoarthritic cartilage. MSCs are a heterogeneous cell population and large inter-donor variation with respect of the chondrogenic potential of these cells has been reported which may hamper clinical application. Presently, prognostic